

## ABSTRACT

A unique HCV RNA molecule is provided having an enhanced efficiency of establishing cell culture replication. Novel adaptive mutations have been identified within the HCV non-structural region that improves the efficiency of establishing persistently replicating HCV RNA in cell culture. This self-replicating polynucleotide molecule contains, contrary to all previous reports, a 5'-NTR that can be either an A as an alternative to the G already disclosed and therefore provides an alternative to existing systems comprising a self-replicating HCV RNA molecule. The G-->A mutation gives rise to HCV RNA molecules that, in conjunction with mutations in the HCV non-structural region, such as the G(2042)C/R mutations, possess greater efficiency of transduction and/or replication. These RNA molecules when transfected in a cell line are useful for evaluating potential inhibitors of HCV replication.